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EXAMINER
COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/934,531	Applicant(s) NIELSEN et al.
	Examiner Brenda Coleman	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 14, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8 and 12-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8 and 12-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☒ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-8 and 12-16 are pending in the application.

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that some of the compounds in Groups II and III may be regarded as adjacent homologues of some of the compounds in Group I and therefore, examination of these Groups together would not be unduly burdensome. This is not found persuasive because a diazacyclooctane, a piperazine and a homopiperazine are clearly structurally dissimilar compound which are classified in various subclasses under classes 540, 544 and 540, respectively.

Note MPEP 2173.05(h) "where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression.

Therefore, what should be considered for patentable distinctness is the compound as a whole. If a reference for one would not be a reference for the other, then restriction is considered proper. Community of properties is not enough to keep homopiperazine, diazacyclooctane and piperazine in the same Markush claim, where the Markush expression is applied only to a portion of a chemical compound. It is the compound as a whole homopiperazine, diazacyclooctane, piperazine, etc., that must be considered for patentable distinctness.

Thus, separate searches in the literature would be required. However, should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The degree of burden on the examiner is high. The class/subclass search on the elected invention where the compounds have a piperazine core would be as follows: class 514, subclasses 218 and class 540, subclass 575 which involved 1268 US patents. The various classes and subclasses mentioned above represent only the degree of burden within the U.S. Patent Classification System, this does not include the search required in the prior art of journal articles and foreign patents.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-8 and 12-14 are rejected as being drawn to an improper Markush group. The recited compounds, while possessing a common utility, differ widely in structure and are not art-recognized equivalents and are thus, independently distinct for the reasons set forth in the restriction above.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on April 26, 1999. It is noted, however, that applicant has not filed a certified copy of the 1999 00571 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5, 7, 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

HOW TO MAKE: In evaluating the enablement question, several factors are to be considered. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman,* 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the invention in the instant case, has claims which embrace substituted homopiperazines. The instant compounds of the formulae wherein the R^1 substituent of the homopiperazine ring is aryl optionally substitute.....; -X-alkyl-Y-alkyl.....; -X-$(alk)_o$-aryl.....; -X-$(alk)_o$-Z.....; - a monocyclic 5 to 6 membered heterocyclic group.....; or an $(alk)_o$-HET.....; etc. are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by claims 1-5. For example where are the starting materials for the preparation of compounds where the homopiperazine ring is substituted with and alkoxyalkoxy. In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

HOW TO USE: Claims 8 and 11-14 are to "a method of treating a disease which is responsive to the activity of nicotinic ACh receptor modulators". Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. However, the specification provides no definitive evidence to correlate any one disorder selected from those disclosed in the specification with the instantly disclosed azacyclooctane derivatives.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed azacyclooctane derivatives. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity

"the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." ***In re Fisher***, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable *in-vivo* physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification does not have working examples on the use of the substituted homopiperazines, etc. The absence of working examples is one of the factors to be considered in deciding whether the practice of an invention would involve undue experimentation. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of "pain, a disease in the central or peripheral, a disease caused by smooth muscle contraction, neurodegeneration, inflammation, chemical substance abuse or withdrawal symptoms caused by the cessation of intake of the chemical substance".

5. Claims 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "treatment ..... chemical substance abuse" cannot be deemed enabled. The notion that a compound could be effective against chemical dependencies in general is contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug addiction" generally. That is because "drug addiction" is not a single disease or cluster of related disorders, but in fact, a

collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine re-uptake site. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find a pharmaceutical to treat chemical addictions generally have thus failed.

6. Claims 8 and 12-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims are not adequately enabled solely based on its inhibitory effect on the nicotinic acetylcholine receptor provided in the specification. Recent studies on experimental and clinical pharmacology of nicotinic acetylcholine receptors cited in Annual Reports in Medicinal Chemistry indicate that the following disorders may be associated with nicotinic acetylcholine receptors: senile dementia of the Alzheimer's type, Parkinson's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, depression, attention deficit disorder, anxiety, dyslexia, schizophrenia, Tourette's syndrome and smoking cessation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is

difficult to treat many of the disorders claimed herein. The "nicotinic" effect with respect to Alzheimer's is hypothesized. Parkinson's Disease is "presently of unknown etiology" and recent studies have exhibited dosing problems as well as "unusually high placebo effects". The pathophysiology of Tourette's Syndrome is unknown. The treatment of ulcerative colitis is currently "limited to anti-inflammatories, immunosuppressants and antibiotics". Additionally, there are other pathological non-CNS conditions, such as pouchitis and influenza virus-induced pneuomonitis, where nicotine efficacy has been reported, but remains to be confirmed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-8 and 12-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claim 1 (and claims dependent thereon) recites a compound represented by the **general** formula (I). A formula is not general when all of the variables are defined. Deletion of "general" is suggested. See line 4 on page 36 and line 32 on page 37.

b) Claim 1 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the definition of R where the monocyclic 5 to 6 membered heterocyclic group is substituted by thioalkynyl, ,. It is not clear what the second comma is for.

c) Claim 1 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the list of substituents for the definition of R where the monocyclic 5 to 6 membered heterocyclic group is substituted one or more times is not stated as a proper Markush group.

d) Claim 1 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the second occurrence of alkynoxy in the list of substituents for monocyclic 5 to 6 membered heterocyclic group in the definition of R^1.

e) Claim 1 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the definition of R^1 where the monocyclic 5 to 6 membered heterocyclic group is substituted by thioalkynyl, ,. It is not clear what the second comma is for.

f) Claim 1 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the list of substituents for the definition of R^1 where the monocyclic 5 to 6 membered heterocyclic group is substituted one or more times is not stated as a proper Markush group.

g) Claim 1 is vague and indefinite in that it is not known what is meant by the capital letter which appears to be the beginning of the last line on page 37.

608.01(m) Form of Claims [R - 3]

The claim or claims must commence on a separate sheet and should appear after the detailed description of the invention.< While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim", "The invention claimed is" (or the equivalent). If, at the time of allowance, the quoted terminology is not present, it is inserted by the clerk. **Each claim begins with a capital letter** and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations. See Fressola v. Manbeck, >36 USPQ2d 1211< (D.D.C. 1995). ** >Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation, 37 CFR 1.75(i).

h) Claims 1-6, 8, 13 and 14 are vague and indefinite in that they do not end with a period indicating the end of the claim.

i) Claim 3 is vague and indefinite in that it is not known what is meant by the definition of R which is "as defined above", however, the definition of R is not in claim 3.

j) Claim 3 recites the limitation "heteroaryl" in the definition of R^1. There is insufficient antecedent basis for this limitation in the claim.

k) Claim 4 is vague and indefinite in that it is not known what is meant by the definition of R^1 where R^1 is pyridyl or pyridinyl which are the same.

l) Claim 4 recites the limitation "alkoxy-epoxy, alkoxyalkenyl, alkoxyalkynyl, thioalkenyl, selenoalkyl, alkoxycycloalkyl, hydroxyalkoxy, thioalkoxy, thioalkylaryl, carboxylamido, a bicyclic heterocyclic group, thioalkoxyaryl, thioaryl, hydroxy, trifluoromethanesulfonyloxy" in the definition of substituents for

quinoline and isoquinoline of R^1. There is insufficient antecedent basis for this limitation in the claim.

m) Claim 4 recites the limitation "alkoxyalkoxy, alkoxy-epoxy, alkoxyalkenyl, alkoxyalkynyl, alkoxycycloalkyl, hydroxyalkoxy, thioalkoxy, thioalkylaryl, a bicyclic heterocyclic group, thioalkoxyaryl, thioaryl, hydroxy, trifluoromethanesulfonyloxy, halogen" in the definition of substituents for pyridyl and pyridazinyl of R^1. There is insufficient antecedent basis for this limitation in the claim.

n) Claim 5 recites the limitation "5-1-butyl-N-methylamino), N-azacyclobutenyl, N-2-pyrrolinyl, N-3-pyrrolinyl, 1,4,5,6-teterahydropyridinyl, 1,2,5,6-tetrahydropyridinyl, homopiperazinyl, 5-propyl-1,2-epoxy-1-oxy, 5-phenylacetylenyl, 2-ethyl-1-butoxy, 1-methyl-1-prop-2-en-oxy, cyclobutylmethoxy, hex-2-en-oxy, 2-methyl-1-prop-1-en-oxy, 1-piperdinyl, N-azacycloheptyl, n-azacycloctanyl, 1-morpholinyl" in the definition of substituents for R^1. There is insufficient antecedent basis for this limitation in the claim.

o) Claim 5 is vague and indefinite in that it is not known what is meant by the moiety for R^1 where R^1 is 1-[5-1-butyl-N-methylamino)3-pyridyl] which contains an unmatched parenthesis.

p) All of the species of claim 6 recites substituents of the homopiperazine ring at the 5 and 3 positions; 6 and 3 positions; at the 5, 6 and 3 positions, etc. There is

insufficient antecedent basis for this limitation in the claim. The only points of substitution of the homopiperazine ring is at the nitrogen atoms.

q) Claim 8 is a substantial duplicate of claims 1-6, as the only difference is a statement of intended use which is not given material weight. Note In re Tuominen 213 USPQ 89.

r) Claim 12 is vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the disorders capable of being treated by modulating the activity of acetylcholine receptors. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the

accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in analgesics, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

s) Regarding claim 13, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

t) Claims 15 and 16 recite the limitation "6-bromo-5-methoxy-3-pyridyl" in the nomenclature of the species. There is insufficient antecedent basis for this limitation in the claim.

u) Claim 16 recites the limitation "N oxide thereof" in addition to the compound. There is insufficient antecedent basis for this limitation in the claim.

v) Claim 16 recites the limitation "labeled or un-labeled form" in addition to the compound. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Stokbroekx et al., EP 0 156 433. Stokbroekx teaches compounds of the instant invention where R is hydrogen and R^1 is 1-(6-chloro-3-pyridazinyl) or 1-(6-chloro-5-methyl-3-pyridazinyl). See compound 215 and 216.

9. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Stokbroekx, EP 0 211 457. Stokbroekx teaches compounds of the instant invention where R is hydrogen and R^1 is 1-(6-chloro-3-pyridazinyl) or 1-(6-phenyl-3-pyridazinyl). See column 10, lines 34-35 and 43-44.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner can normally be reached on Mondays from 8:30 AM to 5:00 PM, on Tuesdays from 8:00 AM to 4:30 PM, on Wednesday thru Friday from 9:00 AM to 5:30 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner AU 1624
April 29, 2003